General

Guideline Title

Cervical screening.

Bibliographic Source(s)

Murphy J, Kennedy E, Dunn S, Fung Kee Fung M, Gzik D, McLachlin CM, Shier M, Paszat L. Cervical screening. Toronto (ON): Cancer Care Ontario (CCO); 2011 Oct 5. Various p. (Evidence-based series; no. 15-9). [122 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Ontario Cervical Screening Program, Gynecology Cancer Disease Site Group. McLachlin CM, Mai V, Murphy J, Fung Kee Fung M, Chambers A. Cervical screening. Toronto (ON): Cancer Care Ontario (CCO); 2005 May 20. 39 p.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

Recommendations for Cervical Screening with Human Papillomavirus (HPV) Deoxyribonucleic Acid (DNA) Testing

Primary Screening Test

HPV DNA testing of cells collected from the cervix is recommended for primary cervical screening. Cytology screening, which was recommended for primary screening in the previous version of this guideline, is now recommended only in the event of a positive HPV DNA test result (see HPV screening algorithm, Figure 1 in the original guideline document). Interim recommendations are provided below, because HPV testing is not funded at this time for primary screening in Ontario.

Age of Screening Initiation

It is the opinion of the Cervical Screening Guideline Working Group (the Working Group) that there is insufficient evidence at this time to make a recommendation for the age at which to begin cervical screening using HPV testing as the primary screen. HPV testing performs better for women 30 and over compared to younger women because the rate of transient infections is higher in the younger age group; therefore, the screening

algorithm in the following recommendation is presented for women 30-65 years of age.

Screening Interval (Women 30-65)

Screening interval recommendations are according to the algorithm presented in Figure 1 in the original guideline document. For women aged 30-65, HPV DNA testing is to occur at five-year intervals after an initial negative result, which is a change from the recommendation for repeat cytology testing every two to three years contained in the 2005 version of this guideline. HPV-positive tests should be assessed with cytology testing and not referred directly to colposcopy. Repeat HPV testing for results of HPV positive/cytology negative should be conducted after one year.

Age of Screening Cessation

Screening may be discontinued after the age of 65 provided there is an adequate negative screening history in the previous 10 years (i.e., two or more negative tests) and a final negative HPV test at age 65. Women who do not meet these requirements should continue with screening at recommended intervals. This is a change from the previous recommendation of cessation at age 70.

Interim Recommendations (to be followed until HPV testing is funded)

Primary Screening Test

On an interim basis, the authors endorse the recommendation contained in the 2005 version of this guideline: primary screening with cytology testing.

Age of Screening Initiation

Cytology testing should commence at 21 years of age for sexually active women.

Screening Interval

Women should be screened every three years.

Age of Screening Cessation

The authors endorse the age of cessation of cytology-based testing presented in the 2005 version of this guideline:

- Screening may be discontinued after the age of 70 if there is an adequate negative cytology screening history in the previous 10 years (i.e., three to four negative cytology tests).

Recommended Management for Women with Abnormal Cytology

Management recommendations were not included in the scope of the current guideline. The algorithm for the management of abnormal results from the previous version of this guideline has been appended, however, as its recommendations still apply to the interim cytology-based guidelines provided here. Please see Appendix 3 (Section 1, page 19) in the original guideline document.

Clinical Algorithm(s)

A clinical algorithm for primary cervical screening with human papillomavirus (HPV) testing in women ages 30-65 is provided in the original guideline document.

Scope

Disease/Condition(s)

Cervical cancer

Guideline Category

Prevention

Screening

Technology Assessment

Clinical Specialty

Family Practice

Internal Medicine

Obstetrics and Gynecology

Oncology

Preventive Medicine

Intended Users

Physicians

Guideline Objective(s)

- To evaluate, in the context of an organized cervical screening program:
  - The optimal primary cervical screening method (i.e., human papillomavirus [HPV] deoxyribonucleic acid [DNA] testing and/or cytology testing)
- To evaluate, for average risk, asymptomatic women:
  - The most appropriate age for the initiation of cervical screening
  - The optimal interval between cervical screenings
  - The most appropriate age for the cessation of cervical screening

Target Population

Average risk, asymptomatic women in Ontario, Canada

Interventions and Practices Considered

Primary cervical screening:

- Cytology testing
- Human papillomavirus (HPV) deoxyribonucleic acid (DNA) testing

Major Outcomes Considered

- Sensitivity and specificity of screening tests
- Rates of unsatisfactory specimens
- Safety/adverse effects of interventions
- Incidence and mortality rates

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

Web sites of international guideline developers, Canadian provincial and national cancer agencies, and CancerViewCanada (www.cancerguidelines.ca) were searched for existing evidence-based practice guidelines. As an initial screen, guidelines were assessed with item seven from the Appraisal of Guidelines for Research and Evaluation (AGREE II) tool, which is part of the Rigour of Development domain, an assessment of whether guideline development included a systematic search for evidence. If guidelines rated highly on this item, they were then to be assessed with the remainder of the questions from the AGREE II Rigour of Development domain (8 items in total). MEDLINE and EMBASE were searched (2005 to November 2010) using the same text words and medical subject headings (MeSH) as were used for the 2005 version of this guideline: cervix, cervical, cancer, carcinoma, screening, and mass screening (as an exploded MeSH term). Search terms related to study design and publication type included clinical trial (text word and publication type), clinical trials (as an exploded MeSH term), meta-analysis (text word and publication type), and systematic review. Reference lists of papers and review articles were scanned for additional citations. The Cochrane Library was searched for topic-specific reviews from 2005 to 2010. The current controlled trials registry (www.controlled-trials.com) was searched to ensure that the most recently published results for the randomized controlled trials (RCTs) were included. For the full literature search, please see Appendix 2 in the original guideline document.

As the development of the guideline neared completion, an additional search of MEDLINE using the key words listed above was conducted to bring the evidence base current to October 2011.

Inclusion Criteria

Eligible sources for the method of primary screening question included the following: practice guidelines, systematic reviews with or without a meta-analysis, and randomized trials. For the questions of age of initiation, age of cessation, and screening interval, cohort and case-control studies were also considered for inclusion in the evidence base. Descriptive studies of the natural history of human papillomavirus (HPV) were also used to inform the recommendations.

Exclusion Criteria

1. Abstracts, letters and editorials
2. Papers published in a language other than English, because of a lack of funding for translation
3. Studies that were designed to assess outcomes in special populations (e.g., high-risk populations)

Number of Source Documents

The systematic review identified nine published guidelines from other Canadian provinces and eight additional guidelines from other countries or organizations that contained recommendations based on a combination of evidence and consensus. In addition, 13 papers reporting results from seven randomized trials either recently completed or underway to assess the use of human papillomavirus (HPV) testing in primary screening were identified. A further seven studies (three case-control, one pooled cohort, two single cohort, and one review article) were identified that address the research questions relating to screening age range and interval. The updated search (November 2010 to October 2011) found one study related to screening interval and one study that provided further results for one of the randomized controlled trials (RCTs) that had previously been identified.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Methods

The Evidence-Based Series (EBS) guidelines developed by the Cancer Care Ontario Program in Evidence-based Care (CCO PEBC) use the methods of the Practice Guidelines Development Cycle. For this project, the core methodology used was the systematic review. Evidence was selected and reviewed by a Research Coordinator from the PEBC and the Cervical Cancer Screening Guideline Working Group (the Working Group) (see Appendix 1 in the original guideline document).

The systematic review is a convenient and up-to-date source of the best available evidence on the research questions listed above. The recommendations developed by the Working Group are published in Section 1 of this Evidence-Based Series report. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

The guideline developers reviewed published cost analyses.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Expert Panel Review and Approval of the Draft Guideline

The Expert Panel comprised members of the Program in Evidence-based Care (PEBC) Gynecologic Cancer Disease Site Group (Gyne DSG), and the Cancer Care Ontario (CCO) Cervical Clinical Advisory Committee (CCAC) who were not already on the Working Group. The Expert Panel was invited to review the draft guideline. Six of 12 members of the CCAC agreed to review the document, and five of these six completed

the review. Of the 11 Gyne DSG members who were asked to participate, six agreed, and five completed the review. Not including relatively minor formatting or wording changes, the comments fell into the broad categories listed below. The Working Group's responses are presented after each comment. A member of CCO's Molecular Oncology Advisory Committee (MOAC) also reviewed the document.

Report Approval Panel (RAP)

Prior to the submission of this Evidence-Based Series (EBS) draft report for External Review, the report was reviewed by the PEBC RAP, a three-person panel whose members have clinical, methodological, and oncology expertise.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC RAP, the Working Group circulated Sections 1 and 2 to external review participants for review and feedback.

Methods

Targeted Peer Review

During the guideline development process, seven targeted peer reviewers from outside Ontario considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Several weeks prior to completion of the draft report, three nominees were contacted by email and asked to serve as reviewers. All three reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on July 7, 2011. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Working Group reviewed the results of the survey.

Professional Consultation

Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Practitioners from the areas of family medicine or primary care, gynecology and those in our database with an interest in human papillomavirus (HPV) testing and/or screening were surveyed. Participants were asked to rate the overall quality of the guideline (Section 1 in the original guideline document) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1 in the original guideline document) and the evidentiary base (Section 2 in the original guideline document). The notification email was sent on July 7, 2011 and the consultation period ended on August 23, 2011. The Working Group reviewed the results of the survey.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Cervical Screening Guideline Expert Panel and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by published guidelines; randomized, case-control, pooled cohort, and single cohort trials; and one review article.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Human Papillomavirus (HPV) Testing

- HPV testing consistently detected significantly more cervical intraepithelial neoplasia grade 2 (CIN2) and CIN3 in the baseline screening round than did cytology-based testing. HPV testing detected fewer CIN2 or more severe (CIN2+) cases in the subsequent screening round, indicating a lead time gain with HPV testing.
- The one trial that had sufficient sample size to report incidence and mortality due to cervical cancer found a significant reduction with HPV testing but not with cytology testing, compared to standard care.
- There was no significant difference in the number of invasive cancers detected in the baseline screening round in the New Technologies in Cervical Cancer trial comparing HPV testing and cytology testing. In the subsequent screening round, no cases of cancer were found in the HPV-testing group, while nine cases were found in the cytology-testing group. A high number of the cancers detected in the second round in the cytology group were adenocarcinomas. This is consistent with previous reports that cytology is less effective in preventing adenocarcinomas than squamous cell carcinomas (approximately 20% of cervical cancers in Ontario are adenocarcinomas).

Cytology Triage of HPV Positive Results

- Due to the higher sensitivity of HPV testing compared to conventional cytology, the rate of colposcopy referral with HPV testing alone is higher than the rate with conventional cytology. For example, in the Canadian Cervical Cancer Screening Trial (CCCaST) randomized controlled trial (RCT), the rate of referral to colposcopy after a positive HPV test alone was 6.1%, compared to a referral rate of 2.6% for conventional cytology results of atypical squamous cells of undetermined significance (ASCUS).
- A triage test can reduce the number of colposcopy referrals and increase the specificity of the screening algorithm. In CCCaST, HPV with Pap triage resulted in a 1.1% rate of referral based on ASCUS. The Finnish Public Health Trial found the frequency of colposcopy referrals was 1.2% in both the conventional cytology arm at a threshold of low-grade squamous intraepithelial lesions (LSIL) and the HPV with cytology triage arm of their trial.

Five-Year Interval after HPV Negative Results

- Six years after a negative HPV test, pooled cohort data found a cumulative incidence rate for CIN3+ of 0.27% (95% confidence interval [CI], 0.12 to 0.45), which was lower than the rate after three years with a negative cytology test (0.51%; 95% CI, 0.23 to 0.77). This indicates that retesting at five-year intervals would entail a low level of risk.
- The risk of CIN3+ after a negative HPV test is low: in a Danish cohort study the 12-year absolute risk of CIN3+ after a negative HPV deoxyribonucleic acid (DNA) test in women with normal cytology was 3.0% (95% CI, 2.5 to 3.5%).

One-Year Interval with HPV Positive/Cytology Negative Results

The short-term persistence of HPV infection for at least one year is an important predictor of CIN2+. In women who tested HPV positive at enrolment and negative after about one year (9-21 months), the cumulative incidence of CIN2+ after three years was 1.2% (95% CI, -0.2 to 2.5). The three-year cumulative incidence of CIN2+ in women who tested positive for carcinogenic HPV at study enrolment and again after approximately one year was 17.0% (95% CI, 12.1 to 22.0). Consequently, referral to colposcopy after two consecutive positive HPV tests occurring a year apart is recommended, even in the event of initially negative cytology results.

Potential Harms

- False-positive and false-negative results of screening tests
- Adverse psychosocial and reproductive outcomes and unnecessary invasive procedures

Qualifying Statements

Qualifying Statements

- The recommendation for human papillomavirus (HPV) testing is applicable only in the context of an organized screening program with an adequate database infrastructure that allows for an invitation to screening at recommended intervals, and a follow-up of women with abnormal test results.
- HPV testing has been shown to be more effective for women 30 years of age and older (see Age of Screening Initiation in the "Major

Recommendations" field).

- Women who have never been sexually active do not require cervical screening. (Sexually active is defined as vaginal intercourse and vaginal/oral and/or vaginal/digital sexual activity.)
- The screening algorithm (see Figure 1 in the original guideline document) should be reviewed for currency prior to implementation. A variation on this algorithm includes genotyping for HPV 16 and/or HPV 18 immediately after a positive HPV test and cytology results of normal, atypical squamous cells of uncertain significance (ASCUS) or low-grade squamous intraepithelial lesion (LSIL), based on the rationale that HPV 16 has been shown to be more persistent and more often associated with high-grade lesions, and HPV 18 is more often associated with difficult to detect lesions in the endocervical canal. Positivity for either of these types may require immediate colposcopy.
- Women with Pap tests that lack transformation zone components (i.e., endocervical and/or metaplastic cells) may continue screening at the regular intervals recommended by the guideline. Repeated samples lacking transformation zone may require further investigation.
- The above statement does not include women with test results of "unsatisfactory" who should undergo repeat screening in three months. This qualifying statement is the opinion of the Working Group based on the clinical experience that a shorter waiting period may result in the detection of reactive changes as a result of the first screening test.
- The Working Group maintains the recommendations for screening of special populations contained in the 2005 guideline:
    - Immunocompromised women (e.g., those currently taking long-term immunosuppressants, those who are human immunodeficiency virus [HIV] positive) should receive annual screening.
    - Screening can be discontinued in women who have undergone a total hysterectomy for benign causes with no history of cervical dysplasia or HPV. Women who have undergone subtotal hysterectomy (with an intact cervix) should continue screening according to the guidelines.
    - Indications for screening frequency for pregnant women should be the same as for women who are not pregnant. Manufacturers' recommendations for the use of individual screening tools in pregnancy should be considered.
    - Women who have sex with women should follow the same cervical screening regimen as women who have sex with men.
- Women who are not sexually active by age 21 may delay cervical screening.
- Women who have never been sexually active do not require cervical screening.
- The interim recommendation to begin screening at 21 years of age should be reviewed within 24 months of the publication of this guideline.
- As HPV-vaccinated women reach the age of screening initiation, there may be impact on the screening recommendations.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Murphy J, Kennedy E, Dunn S, Fung Kee Fung M, Gzik D, McLachlin CM, Shier M, Paszat L. Cervical screening. Toronto (ON): Cancer Care Ontario (CCO); 2011 Oct 5. Various p. (Evidence-based series; no. 15-9). [122 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2005 May 20 (revised 2011 Oct 5)

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Cervical Screening Guideline Working Group

Composition of Group That Authored the Guideline

Working Group Members: Dr. Joan Murphy (*Chair*), Gynecologic Oncologist, Division of Gynecologic Oncology, University Health Network, Toronto; Dr. Sheila Dunn, Family Practitioner, Family Practice Unit, Women's College Hospital, Toronto; Dr. Michael Fung Kee Fung, Director of Gynecologic Oncology Program, Ottawa General Hospital, Ottawa; Dr. Danusia Gzik, Family Practitioner, Regional Primary Care Lead - Cancer Care Ontario, North Simcoe Muskoka Local Health Integration Network; Erin Kennedy, Research Coordinator, Program in Evidence-

based Care, Cancer Care Ontario, Hamilton; Dr. Meg McLachlin, Deputy Chief, Pathology, London Health Sciences Centre, London; Dr. Lawrence Paszat, Senior Scientist, Institute for Clinical Evaluative Sciences, Toronto; Dr. Michael Shier, Director - Colposcopy Unit - Sunnybrook Health Sciences Centre, Toronto

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest (COI) Policy, the guideline authors, Expert Panel members, internal reviewers, and external targeted peer reviewers were asked to disclose potential conflicts of interest.

Four authors declared they had no conflicts. Three others (SD, MFKF, and MS) declared conflicts. SD reported involvement in a clinical trial on this topic. MFKF reported a potential decrease in colposcopy referrals as a result of this guideline. MS reported receiving more than $5000 in a single year from consulting fees, honoraria, and/or other support from GlaxoSmithKline and Graceway Pharmaceuticals, as well as several publications on this topic in the past five years.

For the Expert Panel, six members declared they had no conflicts of interest, and five (LE, AC, MP, JF, TC) declared conflicts. LE reported receiving more than $5000 in a single year from consulting fees, honoraria, and/or other support from the Canadian Partnership Against Cancer for the creation of an economic model from primary prevention to palliation in cervical cancer and publishing on this topic in the past five years. AC and MP have received honoraria for HPV vaccine-related speaking engagements. JF and TC have published on this topic in the past five years or have related publications in press.

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Ontario Cervical Screening Program, Gynecology Cancer Disease Site Group. McLachlin CM, Mai V, Murphy J, Fung Kee Fung M, Chambers A. Cervical screening. Toronto (ON): Cancer Care Ontario (CCO); 2005 May 20. 39 p.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

Availability of Companion Documents

The following are available:

- Cervical screening. Summary. Toronto (ON): Cancer Care Ontario (CCO). 2011 Oct 5. 20 p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario (CCO) Web site.
- Program in Evidence-Based Care (PEBC) handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Electronic copies: Available in PDF from the CCO Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on August 11, 2005. The information was verified by the guideline developer on September 13, 2005. This NGC summary was updated by ECRI Institute on September 6, 2013.

Copyright Statement

Disclaimer

NGC Disclaimer